UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/567,522	11/06/2006	Torsten Neuefeind	MAIWAM10.002APC	1328

20995 7590 09/21/2010

KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER	
HIXSON, CHRISTOPHER	

ART UNIT	PAPER NUMBER
1797	

NOTIFICATION DATE	DELIVERY MODE
09/21/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

jcartee@kmob.com
efiling@kmob.com
eOAPilot@kmob.com

Office Action Summary	Application No.	Applicant(s)	
	10/567,522	NEUEFEIND ET AL.	
	Examiner	Art Unit	
	CHRISTOPHER A. HIXSON	1797	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5,6 and 9-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,6 and 9-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6 April 2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The applicant's amendment filed on 7 July 2010 is acknowledged. Claims 4, 7, and 8 are cancelled. Claims 1-3, 5, 6, and 9-52 are currently pending and are considered on the merits below.

Response to Amendment

2. The examiner modified the grounds of rejection below consistent with the applicant's amendment.

Specification

3. The incorporation of essential material in the specification by reference to an unpublished U.S. application, foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference, if the material is relied upon to overcome any objection, rejection, or other requirement imposed by the Office. The amendment must be accompanied by a statement executed by the applicant, or a practitioner representing the applicant, stating that the material being inserted is the material previously incorporated by reference and that the amendment contains no new matter. 37 CFR 1.57(f). The examiner notes that many of the details of the apparatus which is essential to the claimed method are described by German language documents incorporated by reference.

Claim Rejections - 35 USC § 103

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. **Claims 1-3, 9, 10, 13, 14, 24, 25, 29, 30, 32-35, 44, and 45** are rejected under 35 U.S.C. 103(a) as being unpatentable over Sjogren et al. (Journal of Applied Crystallography 2002)(IDS)(Sjogren) in view of Rossele et al. (Biomacromolecules 2003)(IDS)(Rossele).

Regarding claim 1, Sjogren teaches that he fixed a protein crystal to a holding device such that the crystal was not embedded in a liquid environment (Fig. 1a, "crystal"), generated a gas stream of defined composition around the crystal (p.115, 2.4.1 the wet oxygen or nitrogen stream) which contained a solvent and an additional molecular species having a molecular weight of less than 500 Daltons (nitrogen or oxygen), but which must be volatile (p.115, 2.4, "[t]he vapour-stream apparatus," for example, since only vapor passes by the crystal in the apparatus, only vaporizable compounds are candidates).

Sjogren does not teach that he applied his solvent or additional molecular species to the crystal in the form of droplets.

Rossele teaches that he created an apparatus which is capable of ejecting microdroplets of a fluid towards a crystal (p.981, "Microdrop Generation," and Fig. 1a, dispensing head), and that the crystal absorbs the contents of the droplets in such a way as to alter the crystal (p.984, "Discussion," where x-ray features revealed crystallographic changes in the substance under study after droplets were applied).

It would have been obvious to one of ordinary skill in the art at the time of invention to have modified Sjogren's method to incorporate the microdroplet generator of Rossele, since Rossele supplies microdroplets which were shown to penetrate the crystal to the extent of altering the observed crystal structure capable of bearing any dissolved substance (without regard to volatility) which would allow Sjogren's method to be performed using a wider variety of ligands.

Regarding claims 2 and 3, Sjogren indicates that among the molecules he would use, is ammonium acetate (p.116, col. 1, lines 1-10), which is less than 100 Daltons.

Regarding claim 9, Sjogren's gas stream has controlled humidity (p.115, 2.4.1 the wet oxygen or nitrogen stream).

Regarding claim 10, both Sjogren and Rossele teach that a regulated gas stream is important to their methods (Sjogren indicates this since he regulates that humidity of his stream, p.115, 2.4.1 the wet oxygen or nitrogen stream, and Rossele regulates his stream during the drip-on procedure, since the droplets humidify the air surrounding

them as they leave the nozzle of the microdrop generator on their way to the mounted crystal, p.981, "Microdrop generation").

Regarding claims 13 and 14, Rossele teaches that his microdrops have a volume of 65 pL (p.981, col. 1). This means that the drops are smaller than the volume of the crystal (not least because claim 14 which depends on claim 13 recites the range 4 pL - 1 nL and the size of the droplets anticipates the range of 4 pL - 1 nL recited in claim 14).

Regarding claim 24, Sjogren's gas stream contains one or more substances (Sjogren indicates this since he regulates that humidity of his stream, p.115, 2.4.1 the wet oxygen or nitrogen stream).

Regarding claim 25, Sjogren irradiates the crystal with X-ray radiation and records the diffraction image of the crystal (Fig. 2).

Regarding claim 29, both Sjogren and Rossele teach that they record diffraction data during the treatment process (Sjogren, Fig. 2, and Rossele p.981, "X-ray diffraction setup"). Rossele explicitly indicates that he uses monochromatic X-ray radiation.

Regarding claim 30, the combined method of Sjogren and Rossele includes the step of applying at least one molecular species to the crystal according to claim 1, Rossele measures diffraction intensities as a function of time, and his intensities are compared with respect to their time-dependent sequence (p.981, "X-ray diffraction setup" and Fig. 4).

Rossele does not seem to explicitly teach that his intensities are measured at intervals with a variable length.

As long as the intervals are small enough to capture the physics of interest, the length of the interval does not affect the result. Consequently, one of ordinary skill in the art would appreciate that the interval could be obviously changed to be of variable length in order to optimally capture data of interest.

Regarding claim 32, Rossele teaches that he includes a device for treating a crystal with a substance having a holder (p.982, col. 1) for fixing the crystal and at least one micro dosage system (p.981, "Microdrop generation") which is arranged in relation to the holder such that it can apply microdrops of the liquid onto the crystal fixed in the holder (Fig. 1).

Regarding claim 33, Sjogren's method includes the use of a device capable of generating a defined environment around the crystal (Fig. 1a and caption).

Regarding claim 34, Sjogren's method uses a device which generates a defined environment by generating a gas stream of defined composition around the crystal (Fig. 1a and caption).

Regarding claim 35, Sjogren's holder is laid out such that the gas stream and be led through the holder in such a way that it is directed toward the crystal fixed in the holder (Fig. 1a).

Regarding claims 44 and 45, Rossele teaches that his microdrops have a volume of 65 picoliters (p.981, col. 1). This means that the drops are smaller than the volume of the crystal (not least because claim 14 which depends on claim 13 recites the range 4 pL - 1 nL). This makes the drops inherently having a volume between 5%-20% of the crystal's volume, as a typical protein crystal's volume is measured in microliters.

6. **Claims 5, 26, and 28** are rejected under 35 U.S.C. 103(a) as being unpatentable over Sjogren in view of Rossele as applied to claims 1-3, 9, 10, 13, 14, 24, 25, 29, 30, 32-35, 44, and 45 above, and further in view of Nienaber et al. (Nature Biotechnology 2000)(IDS)(Nienaber).

Regarding claim 5, Sjogren teaches that an alternative to his method of introducing molecular species to a protein crystal is a soaking technique (p.116, 2.4.3).

However, neither Sjogren nor Rossele seem to explicitly indicate that the solutions they apply to their crystals bind to proteins in a protein crystal as ligands with an affinity between 10^{-3} and 10^{-4} M.

Nienaber teaches that the soaking technique mentioned by Sjogren is useful for introducing ligands to a protein crystal for the purpose of providing data to drug discovery efforts aimed at designing enzyme inhibitors since such inhibitors depend on binding to the active site of a protein (p.1105 in its entirety). In Nienaber's paper, he indicates that he provided several ligands that bind with affinities in the claimed range (Fig. 2 caption, where one binds at 137 micromolar and the other at 2.5 micromolar).

It would have been obvious to one of ordinary skill in the art to have substituted Nienaber's soaking technique with the combined microdroplet coating technique proposed by the examiner's combination of Sjogren and Rossele described above, for several reasons. First, Rossele's method was used to provide kinetic data regarding the change in crystal structure due to the crystal's hydration, and such an experiment provides more information than merely soaking a crystal and then taking a measurement, since relative binding/displacement of ligands could be observed during the process of soaking. Additionally, such a modification would have been obvious since it would have involved a substation of a known technique for another known technique with a reasonable expectation of success, since both Sjogren and Rossele record changes to crystal structures in the practice of their method, and adding the ligands taught by Nienaber would not change that expectation.

Regarding claim 26, neither Sjogren nor Rossele seem to explicitly teach that they calculate an electron density map using the phase information and the intensity of the reflexes in the diffraction image and determine the binding site and positioning of the molecular species (however, such a teaching may very well be implicit).

Nienaber does explicitly teach that he calculates an electron density map using the phase information and intensity of the reflexes in the diffraction image (p.1107, "Experimental protocol") and determines the binding site and positioning of the molecular species (p.1106, col. 2) as his crystal structure solution methodology.

It would have been obvious to one of ordinary skill in the art at the time of invention to have modified the Sjogren and Rossele combination to calculate an electron density map in the claimed way which determines the binding site and positioning of a bound molecular species as a way of solving the crystal structure of the ligated protein crystal using a conventional technique.

Regarding claim 28, Nienaber, in his crystal structure solving strategy described in claim 26, also determines the binding site and positioning of the molecular species using the difference of electron densities of the non-complex and complexed structures by means of an electron density difference map (Figs. 1 and 2 and p.1107, "Experimental protocol").

7. **Claim 6** is rejected under 35 U.S.C. 103(a) as being unpatentable over Sjogren in view of Rossele as applied to claims 1-3, 9, 10, 13, 14, 24, 25, 29, 30, 32-35, 44, and 45 above, and further in view of Hasnain et al. (Journal of Synchrotron Radiation 1999)(Hasnain).

Regarding claim 6, neither Sjogren nor Rossele seem to explicitly teach that any of the molecules contained in their solution have at least one electron-rich or anomalous dispersion center.

Hasnain teaches that lanthanides incorporated into protein complexes are used to aid in determining the crystal structure of a protein (p.858, col. 2).

It would have been obvious to one of ordinary skill in the art at the time of invention to have modified the combined method taught by Sjogren and Rossele to include delivery of an electron-rich dispersion center in order to improve the quality of their crystallographic analysis' mathematical solution.

8. **Claims 11, 12, 15, 16, 18, 19, 36-43, and 46-51** are rejected under 35 U.S.C. 103(a) as being unpatentable over Sjogren in view of Rossele as applied to claims 1-3, 9, 10, 13, 14, 24, 25, 29, 30, 32-35, 44, and 45 above, and further in view of Kiefersauer et al. (Journal of Applied Crystallography 2000)(Kiefersauer).

Regarding claim 11, nethier Sjogren nor Rossele appear to explicitly teach that they control or synchronize the humidity of the gas stream or the frequency at which the drops are dripped onto the crystal in such a way that the crystal is strained as little as possible such that the volume of the crystal alters by no more than 20%.

Kiefersauer teaches that humidity and temperature of a gas stream can be regulated by a computer to achieve desirable effects on the protein crystal (p.1224, col. 1). He does this in order to ensure that the crystal is in a suitable state for his planned experiments. He further indicates that he can manipulate the gas stream to affect the crystal's volume by as much as 17% (p.1227, col. 1).

It would have been obvious to one of ordinary skill in the art at the time of invention to modify the combined method taught by Rossele and Sjogren to control the

humidity of the gas stream and the frequency of the droplet stream (since that too affects the humidity and hydration quality of the crystal) since Kiefersauer indicates that these factors affect the volume of quality of the crystal.

Regarding claim 12, Kiefersauer also teaches that he includes a solubilizer at a controlled concentration (saturated methanol or formaldehyde, p.1227, col. 1, 3.2.2). Rather than applying these solvents via the gas phase, it would have been obvious to try applying them in the form of microdroplets, as Rossele teaches to do to hydrate a crystal, since Rossele teaches that the droplets are an effective way to hydrate his crystal.

Regarding claim 15, 16, 18, and 19, Kiefersauer teaches that he applies humid air and methanol to the crystal (p.1227, col. 1, 3.2.2). He also teaches that the temperature of his gas stream should be a few degrees above room temperature (ie, above 20C). Rather than applying these solvents via the gas phase, it would have been obvious to try applying them in the form of microdroplets, as Rossele teaches to do to hydrate a crystal since Rossele teaches that the droplets are an effective way to hydrate his crystal.

Regarding claims 36-38, neither Sjogren nor Rossele seem to explicitly teach that the method uses a device having a holder consisting of a carrier block for a holder capillary, which has a free support end for the crystal, is used, where the holder capillary is a micropipette in which a negative pressure can be generated in order to hold the crystal, and where the carrier block of the device has an integrated gas channel having a mouth end, which is directed toward the support end of the holder capillary.

Kiefersauer teaches that his method uses a device having a holder consisting of a carrier block (Fig. 2, "insert") for a holder capillary ("micropipette", Fig. 2, attached to a vacuum line), which has a free support end for the crystal, is used, and where the carrier block of the holder of the device has an integrated gas channel having a mouth end, which is directed toward the support end of the holder capillary (Fig. 2, where the gas channel is described in the caption).

It would have been obvious to one of ordinary skill in the art at the time of invention to have modified the combined method of Sjogren and Rossele such that they

incorporate the above described apparatus, because the used of this structure already known in the prior art is a simple substitution which one of ordinary skill in the art would have a great deal of anticipated success.

Regarding claims 39 and 40, neither Sjogren nor Rossele seem to explicitly teach that a device is used which has a gas mixing device, capable of variably adjusting the composition of the gas stream, and wherein the gas consists of air having a specific humidity content and the gas mixing device is capable of adjusting the air humidity.

Kiefersauer teaches that in his method he uses a device which has a gas mixing device, capable of variably adjusting the composition of the gas stream, and where his gas consists of air having a specific humidity content and the gas mixing device is capable of adjusting the air humidity (p.1223 col. 2 - p.1224, col. 1).

It would have been obvious to one of ordinary skill in the art at the time of invention to have performed the method such that a device is used which has a gas mixing device, capable of variably adjusting the composition of the gas stream, and wherein the gas consists of air having a specific humidity content and the gas mixing device is capable of adjusting the air humidity in order to maintain the crystal in conditions suitable for the intended experiment.

Regarding claims 41 and 42, neither Sjogren nor Rossele seem to explicitly teach that a device is used which comprises a device for adding a solubilizer capable of adding to the gas stream a solubilizer for a substance to be introduced into the crystal structure of the crystals, and which further comprises a concentration adjusting device for adjusting the concentration of the solubilizer.

Kiefersauer teaches that in his method he uses a device which comprises a device for adding a solubilizer capable of adding to the gas stream a solubilizer for a substance to be introduced into the crystal structure of the crystals (p.1227, col. 1 "3.2.2 Special gases"), and which further comprises a concentration adjusting device for adjusting the concentration of the solubilizer (p.1227, col. 1 "3.2.2 Special gases", "regulated by a valve") for the benefit of preparing the crystal in a manner suitable for the intended experiment.

Regarding claim 43, neither Sjogren nor Rossele seem to explicitly teach that a device is used which comprises a temperature regulating device capable of variably adjusting the temperature of the gas stream.

Kiefersauer teaches that in his method a device is used which comprises a temperature regulating device capable of variably adjusting the temperature of the gas stream (p.1224, col. 2, "heating element and temperature sensor") for the benefit of preparing the crystal in a manner suitable for the intended experiment.

It would have been obvious to one of ordinary skill in the art at the time of invention to perform the method wherein a device is used which comprises a temperature regulating device capable of variably adjusting the temperature of the gas stream in order to prepare the crystal in a manner suitable for the intended experiment.

Regarding claim 46, Rossele teaches that his microdrops have a volume of 65 pL (p.981, col. 1).

Regarding claims 47-49, Rossele teaches that his method uses a device in which the microdosage system is developped in such a way that it comprises a piezo pipette (p.981, "Microdrop generation") which can be generated in time-controled manner (p.981, col. 2, controlled by software).

However, Rossele does not teach that his system is capable of supplying different liquids or that it is electrically controllable with electrically controllable valves with different liquid supply containers.

Kiefersauer teaches that in his method, water and methanol are required to prepare the crystal for the intended experiment (p.1227, "3.2.2 Special gases") in the same stream. Consequently, one of ordinary skill in the art would have understood to design the system such that it could deliver said species in the manner described in the instant claims.

It would have been obvious to one of ordinary skill in the art to have performed the method wherein the system is capable of supplying different liquids or that it is electrically controllable with electrically controllable valves with different liquid supply containers in order to prepare the crystal for the intended experiment.

Regarding claim 50, nethier Sjogren nor Rossele seem to explicitly teach that the crystal is vapor-plated with solvent, in particular with organic solvent, by means of an evaporator.

Kiefersauer teaches that in his method the crystal is vapor-plated with solvent, in particular with organic solvent, by means of an evaporator (p.1227, "3.2.2 Special gases") for the benefit of introducing a ligand in a non-destructive manner.

It would have been obvious to one of ordinary skill in the art at the time of invention to have performed the method wherein the crystal is vapor-plated with solvent, in particular with organic solvent, by means of an evaporator in order to introduce a ligand in a non-destructive manner.

Regarding claim 51, the previously proposed combination of Sjogren and Rossele teaches to hold one or more crystals ready (p.982, col. 1), to apply microdrops of a solution containing one or more molecular species, where the molecular species has a molecular weight of less than 500 Daltons, onto the preferably freely mounted crystals and to examine the crystals X-ray crystallographically (p.981, col. 2— p.982, col. 1).

However, neither reference teaches to store the crystals after their treatment before the analysis.

Kiefersauer teaches to store the crystals after treatment (p.1227, col. 2, paragraph 2-3) for the benefit of maintaining the crystal for study after it has been prepared.

Thus it would have been obvious to one of ordinary skill in the art at the time of invention to have stored the treated crystals in order to maintain the crystal for study after it has been prepared.

9. **Claim 17** is rejected under 35 U.S.C. 103(a) as being unpatentable over Sjogren in view of Rossele and Kiefersauer as applied to claims 11, 12, 15, 16, 18, 19, 36-43, and 46-51 above, and further in view of Nienaber.

Regarding claim 17, neither Sjogren, Rossele, nor Kiefersauer seem to explicitly teach that they use DMSO as a solvent.

Nienaber, however, uses DMSO to dissolve fragments intended for use in drug discovery applications by soaking a protein crystal followed by subsequent X-ray analysis ("Experimental protocol", p.1107). Combined with the teachings used to reject claim 16 above, one of ordinary skill in the art would have predicted a reasonable chance of success of performing the analysis described by Nienaber using a humidified droplet application scheme, because both Rossele and Kiefersauer indicate methods than can be used to incorporate molecules of interest (water or methanol, for example) into a protein crystal using vapor and/or microdroplets for the benefit of preparing the crystal in a state suitable for the intended analysis.

It would have been obvious to one of ordinary skill in the art at the time of invention to have performed the method wherein the solvent consists of or contains DMSO in order to prepare the crystal in a state suitable for the intended analysis.

10. **Claims 20-22** are rejected under 35 U.S.C. 103(a) as being unpatentable over Sjogren in view of Rossele as applied to claims 1-3, 9, 10, 13, 14, 24, 25, 29, 30, 32-35, 44, and 45 above, and further in view of Kiefersauer and Nienaber.

Regarding claims 20-22, neither Sjogren nor Rossele seem to explicitly teach that the molecules contained in the solution to be applied onto the crystal are hardly water-soluble, that the solution contains a cocktail of at least 3 different molecule species, or that the solution contains at least one molecule species at a concentration of 0.001 - 0.1 M.

Kiefersauer teaches that soaking crystals destroys the crystals, even when supplied with a low concentration of methanol (p.1227, "3.2.2 Special gases"). Thus one of ordinary skill would have been motivated to introduce compounds intended to be incorporated into a crystal by means other than soaking. Combined with the teaching of Rossele, indicating that water droplets become incorporated into protein crystals, one of ordinary skill in the art would have predicted a reasonable chance of success of incorporating species dissolved in droplets in to a protein crystal for the benefit of preparing the crystal in a manner suitable for the intended experiment, and that this

approach would have been preferable to soaking, which as taught by Kiefersauer is prone to damaging the crystal.

It would have been obvious to spray droplets of a solvent containing dissolved species as a way in incorporating said species into the protein crystal in order to prepare the crystal in a manner suitable for the intended experimentation.

However, this proposed prior art combination does not teach that the molecules contained in the solution to be applied onto the crystal are hardly water-soluble, where the solution contains a cocktail of at least 3 different molecule species, and wherein the solution contains at least one molecule species at a concentration of 0.001 - 0.1 M.

Nienaber teaches that a protein crystal is soaked in a DMSO solution containing 6-8 different species at a concentration of about 0.1 M (p.1107, "Experimental details," col .2) for the benefit of preparing the crystal in a state suitable for the intended analysis. These species are soluble in DMSO, but as listed on p.1106, col. 2, are sparingly soluble in water.

It would have been obvious to one of ordinary skill in the art at the time of invention to have performed the method wherein the molecules contained in the solution to be applied onto the crystal are hardly water-soluble, where the solution contains a cocktail of at least 3 different molecule species, and wherein the solution contains at least one molecule species at a concentration of 0.001 - 0.1 M in order to prepare the crystal in a state suitable for the intended analysis.

11. **Claims 23 and 52** are rejected under 35 U.S.C. 103(a) as being unpatentable over Sjogren in view of Rossele as applied to claims 1-3, 9, 10, 13, 14, 24, 25, 29, 30, 32-35, 44, and 45 above, and further in view of Erlanson et al. (Journal of Medicinal Chemistry 2004)(Erlanson).

Regarding claims 23 and 52, neither Sjogren nor Rossele seem to teach the preliminary step of identifying fragments that potentially bind to a target structure using a spectroscopic method.

Erlanson teaches that NMR can be used to screen ligands for binding affinity to a protein (p.3465) for the benefit of selecting interesting fragments for study. This step is

especially considered a preliminary step because crystallography is generally considered a more arduous technique (p.3466, col. 2, "2.4 Crystallography-based approaches").

It would have been obvious to one of ordinary skill in the art at the time of invention to have performed the method including the preliminary step of identifying fragments that potentially bind to a target structure using a spectroscopic method, such as NMR, in order to select interesting fragments for study.

12. **Claims 23 and 52** are rejected under 35 U.S.C. 103(a) as being unpatentable over Sjogren in view of Rossele as applied to claims 1-3, 9, 10, 13, 14, 24, 25, 29, 30, 32-35, 44, and 45 above, and further in view of Huth et al. (Combinatorial Chemistry and High Throughput Screening 2002)(Huth).

Regarding claims 23 and 52, neither Sjogren nor Rossele seem to teach the preliminary step of identifying fragments that potentially bind to a target structure using a spectroscopic method for the benefit of selecting interesting fragments to study.

Huth teaches that NMR can be used to screen ligands for binding affinity to a protein (abstract) for the benefit of selecting interesting fragments for study.

It would have been obvious to one of ordinary skill in the art at the time of invention to have performed the method including the preliminary step of identifying fragments that potentially bind to a target structure using a spectroscopic method, such as NMR, in order to select interesting fragments for study.

13. **Claim 27** is rejected under 35 U.S.C. 103(a) as being unpatentable over Sjogren in view of Rossele and Nienaber as applied to claims 5, 26, and 28 above, and further in view of Hasnain.

Regarding claim 27, neither Sjogren, Rossele, nor Nienaber seem to explicitly teach teach wherein the phase information is obtained using heavy metal atom derivatives, "molecular replacement", or MAD.

Hasnain teaches to obtain phase information using MAD (p.858, "4.2 Early experiments and their impact on MAD") for the benefit of solving the phase problem in protein crystallography.

It would have been obvious to one of ordinary skill in the art at the time of invention to perform the method wherein the phase information is obtained using heavy metal atom derivatives, "molecular replacement", or MAD in order to solve the phase problem.

14. **Claim 31** is rejected under 35 U.S.C. 103(a) as being unpatentable over Sjogren in view of Rossele as applied to claims 1-3, 9, 10, 13, 14, 24, 25, 29, 30, 32-35, 44, and 45 above, and further in view of Kiefersauer, Nienaber, and Erlanson.

Kiefersauer teaches that soaking crystals destroys the crystals, even when supplied with a low concentration of methanol (p.1227, "3.2.2 Special gases"). Thus one of ordinary skill would have been motivated to introduce compounds intended to be incorporated into a crystal by means other than soaking. Combined with the teaching of Rossele, indicating that water droplets become incorporated into protein crystals, one of ordinary skill in the art would have predicted a reasonable chance of success of incorporating species dissolved in droplets in to a protein crystal for the benefit of preparing the crystal in a manner suitable for the intended experiment, and that this approach would have been preferable to soaking, which as taught by Kiefersauer is prone to damaging the crystal.

Thus it would have been obvious to spray droplets of a solvent containing dissolved species as a way in incorporating said species into the protein crystal in order to prepare the crystal in a manner suitable for the intended experimentation.

However, the prior art combination does not teach wherein fragments are incorporated into the crystal.

In the same field of endeavor of protein crystallography, Nienaber teaches to soak a crystal with fragments to determine binding. It further teaches determining the structure of at least one complex having at a fragment bound (p.1106, col. 2) for the benefit of determining candidates for inhibitors.

Thus it would have been obvious to one of ordinary skill in the art at the time of invention to have determined the structure of at least one complex having a fragment bound in order to determine candidates for inhibitors.

However, the prior art combination does not teach wherein the structure of one complex having at least two fragments is determined, where linkers are determined, and the synthesis of the ligand containing the two fragments and the linker is performed.

In the same field of endeavor of drug discovery, Erlanson teaches determining the structure of one complex having at least two fragments, determining a linker, and synthesizing the final ligand (p.3467, col. 1, first paragraph) for the benefit of developing a drug candidate.

Thus it would have been obvious to one of ordinary skill in the art at the time of invention to have determined the structure of one complex having at least two fragments, determining a linker, and synthesizing a final ligand in order to develop a drug candidate.

15. **Claim 31** is rejected under 35 U.S.C. 103(a) as being unpatentable over Sjogren in view of Rossele as applied to claims 1-3, 9, 10, 13, 14, 24, 25, 29, 30, 32-35, 44, and 45 above, and further in view of Kiefersauer, Nienaber, and Huth.

Kiefersauer teaches that soaking crystals destroys the crystals, even when supplied with a low concentration of methanol (p.1227, "3.2.2 Special gases"). Thus one of ordinary skill would have been motivated to introduce compounds intended to be incorporated into a crystal by means other than soaking. Combined with the teaching of Rossele, indicating that water droplets become incorporated into protein crystals, one of ordinary skill in the art would have predicted a reasonable chance of success of incorporating species dissolved in droplets in to a protein crystal for the benefit of preparing the crystal in a manner suitable for the intended experiment, and that this approach would have been preferable to soaking, which as taught by Kiefersauer is prone to damaging the crystal.

Thus it would have been obvious to spray droplets of a solvent containing dissolved species as a way in incorporating said species into the protein crystal in order to prepare the crystal in a manner suitable for the intended experimentation.

However, the prior art combination does not teach wherein fragments are incorporated into the crystal.

In the same field of endeavor of protein crystallography, Nienaber teaches to soak a crystal with fragments to determine binding. It further teaches determining the structure of at least one complex having at a fragment bound (p.1106, col. 2) for the benefit of determining candidates for inhibitors.

Thus it would have been obvious to one of ordinary skill in the art at the time of invention to have determined the structure of at least one complex having a fragment bound in order to determine candidates for inhibitors.

However, the prior art combination does not teach wherein the structure of one complex having at least two fragments is determined, where linkers are determined, and the synthesis of the ligand containing the two fragments and the linker is performed.

In the same field of endeavor of drug discovery, Huth teaches determining the structure of one complex having at least two fragments, determining a linker, and synthesizing the final ligand (Fig. 1) for the benefit of developing a drug candidate.

This it would have been obvious to one of ordinary skill in the art at the time of invention to have determined the structure of one complex having at least two fragments, determining a linker, and synthesizing a final ligand in order to develop a drug candidate.

Response to Arguments

16. Applicant's arguments have been considered but are moot in view of the new ground(s) of rejection.

Nonetheless, the examiner will comment on some of the remarks made by the applicant that still have relevance (though the examiner fully considered all of the arguments). For example, the applicants argue that since Rossele was published less than one year before the filing date of the instant application's *foreign* priority

documents, that a rejection under 35 USC 102(b) was inappropriate. However, as the text of 35 USC 102(b) clearly indicates, such a rejection is appropriate when using a reference published "more than one year prior to the date of application for patent in the United States" (see 35 USC 102(b), emphasis added by examiner). Since the foreign priority documents do not establish the date of filing in the United States, such an argument is clearly made in error. Accordingly, the examiner does not agree that Rossele should have been applied only under 35 USC 102(a) based on his understanding of the applicable statutes.

Regarding Erlanson, the applicants argue that since the Erlanson document was published after the foreign priority dates, it is not available as a reference to the examiner for the purposes of prior art. However, the applicant cannot rely upon the foreign priority papers to overcome rejections based on this document because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Regarding Nienaber, the applicants argue that this document teaches away from the microdroplet coating technique, since it is directed to an alternative technique of soaking. However, nowhere in Nienaber does the reference disparage a microdroplet coating technique. As such, it merely presents an alternative method. The applicant is reminded that "[t]he prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed...." In re Fulton, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004). See MPEP § 2123(II).

Conclusion

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHRISTOPHER A. HIXSON whose telephone number is (571)270-5027. The examiner can normally be reached on M-F 8 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Vickie Kim can be reached on (571)272-0579. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

9/15/2010

/Yelena G. Gakh/
Primary Examiner, Art Unit 1797

cah